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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/896,811	06/29/2001	Thomas D. Madden	16303-008020	7024

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EXAMINER
OSTRUP, CLINTON T

ART UNIT	PAPER NUMBER
1614	9

DATE MAILED: 04/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/896,811	Applicant(s) MADDEN ET AL.	
	Examiner Clinton Ostrup	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-2 and 4-23 are pending in this application.

Priority

Priority to U.S. Provisional Application Numbers 60/264,616, filed January 26, 2001, and 60/215,556 filed June 30, 2000 has been acknowledged.

Response to Applicant's Arguments/Amendment

Specification

Applicants' amendment filed January 27, 2003, Paper No. 7, has made the objection to the disclosure moot. Therefore, the said objection has been withdrawn.

Claim Objections

Applicants' amendment filed January 27, 2003, Paper No. 7, has made the objection to claims 1-2, 10-11, 16, and 21 moot. Therefore, the said objection has been withdrawn.

Double Patenting

Applicants' request filed January 27, 2003, Paper No. 7, that the Obviousness-Type Double Patenting rejection be held in abeyance is noted, however, all reasonable rejections are made. Applicants may hold their response to this rejection in abeyance until allowable subject matter has been indicated; however, the said rejection has been MAINTAINED for the reasons indicated in Paper No. 5, mailed July 22, 2002.

Claim Rejections - 35 USC § 101

Applicants' cancellation of Claims 24-25 in Paper No. 7, filed January 27, 2003, has made the rejection of claims 24-25 under 35 U.S.C. 101, moot. Therefore, the said rejection has been withdrawn.

Claim Rejections - 35 USC § 112

Applicant's arguments filed January 27, 2003, Paper No. 7, to the rejection of claims 9 and 12 under 35 U.S.C. 112, second paragraph have been fully considered. However, the arguments are not found persuasive. Therefore, the said rejection has been MAINTAINED for the reasons set forth in Paper No. 5, mailed July 22, 2002 and those found below.

Applicants' argue that the term "trace amounts or greater" is definite. Applicants cite *In re Borowski* and argue that requirement of "precision and definiteness" has been met. Applicants cite a dictionary definition defining trace amounts as "an extremely small amount," which is also indefinite language. The term extremely small amount is a relative term, and said extremely small amount would depend upon the referenced amount. Applicants then argue that a person skilled in the art would immediately realize the definition meaning an extremely small amount as an amount that may not be detectable using standard assay techniques.

Applicant has claimed "trace amounts or greater" which is inclusive of the term "trace amounts," and since as admitted by applicant, "trace amounts" cannot be detected by standard assay techniques, the claims would include amounts not detected, thus the metes and bounds of "trace amounts or greater" has not been defined. If the

amount is "extremely small" and has not been detected by standard assay techniques, it is impossible to determine whether the "extremely small amount" is within the scope of the claim. Thus, the term "trace amounts or greater" is not clearly defined and the meets and bounds of what constitutes "trace amounts or greater" are not defined with precision and definiteness as required by 35 U.S.C. 112, second paragraph.

Applicants' cancellation of Claims 24-25 in Paper No. 7, filed January 27, 2003, has made the rejection of claims 24-25 under 35 U.S.C. 112, second paragraph, moot. Therefore, the said rejection has been withdrawn.

Claim Rejections - 35 USC § 103

Response to Applicant's Arguments/Amendment

Applicant's arguments filed January 27, 2003, Paper No. 7, to the rejection of claims 1-2 4-23 under 35 U.S.C. 103(a) have been fully considered. However, the arguments are not found persuasive and the said rejection has been MAINTAINED.

Applicants argue that the claimed formulation of claim 1 is surprisingly efficacious, as seen in Figure 5 and page 20, lines 28-32 of the specification. However, the claimed invention is not commensurate with the amounts described in the specification or Figure 5. The amounts claimed are mg/M^2/dose and the amounts in the specification and Figure 5 are mg/kg. Since the claimed amounts would depend upon the M^2 of the patient, not the weight as shown in the "surprisingly efficacious" results, these arguments are not convincing because they are not commensurate with what is being claimed. Furthermore, only claims 1-2, 4-5, and 13-15 require the specific formulation of claim 1.

Applicants then argue that Slater et al do not teach the advantages of a liposome comprised of sphingomyelin and cholesterol and that based on the results of Slater et al., a skilled artisan would not have been motivated to use a lower dosage level of topotecan as claimed in the instant invention because Slater et al., showed poor efficacy at low dosage of liposomal topotecan. The claimed amounts depend on the size, not the weight of the person; therefore the results compared are not commensurate with the instantly claimed subject matter.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Moreover, the examiner cited NEXSTAR, which specifically teaches that cholesterol is known to improve stability and prevent loss of phospholipid to lipoproteins *in vivo*. Slater et al., taught that sphingomyelin may be used as a vesicle-forming lipid and that a preferred liposome contain 5-60 mole percent cholesterol.

NEXSTAR teaches phospholipid to cholesterol ratios, which overlap those of instant claim 4. Thus, it would have been obvious to one having ordinary skill in the art at the time the invention was made to add cholesterol as taught by both the primary and secondary references in amounts taught by the secondary reference because of the expectation of obtaining a liposomal formulation with improved stability and which prevents phospholipid loss to lipoproteins in vivo.

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 112

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 9 and 12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phraseology "trace amounts or greater" in claims 9 and 12, is a relative phrase which renders the claim indefinite. The phrase " trace amounts or greater " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of this claim are unascertainable because it is unclear what the lower limit of "trace amounts or greater" includes or excludes.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-2 and 4-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater et al., 6,355,268 and further in view of NEXSTAR PHARMACEUTICALS, INC., WO 99/13816 (NEXSTAR).

Slater et al., disclose liposome-entrapped topoisomerase inhibitors including camptothecin and camptothecin analogs such as topotecan and irinotecan. See: col. 1,

lines 42-52, col. 2, line 65 – col. 3, line 15. The reference teaches that the liposome formulations remain in the blood stream for prolonged periods of time and retains the drugs antitumor activity. See: col. 2, lines 37-43 and abstract. The primary reference teaches vesicle forming lipids in an amount between about 1-20 mole percent and having entrapped within the liposome a topoisomerase I/II inhibitor at a concentration of about 0.10-0.20 μmole drug per μmole lipid. See: col. 2, lines 45-64.

Slater et al., teach the vesicle-forming lipid as hydrogenated soy phosphatidylcholine, distearoyl phosphatidylcholine or sphingomyelin and other suitable lipids, including glycolipids and sterols such as cholesterol, can be used as vesicle forming lipids. See: col. 3, lines 30-68. The reference teaches that the effective amount of the topoisomerase can vary depending on factors known to those skilled in the art and one skilled in the art would be able to consider such factors and make a determination regarding the effective amount. See: col. 5, lines 34-64.

The primary reference teaches that encapsulation of camptothecin and its analogs, which have a α-hydroxy lactone ring which hydrolyzes in aqueous environments, is stabilized by entrapping these compounds in a liposome. Furthermore, Slater et al., specifically teach that the prior art has shown that a liposome-entrapped formulation of topotecan is stabilized and hydrolysis of the lactone ring is inactivated. See: col. 1, line 53 – col. 2, line 23. The primary reference also teaches that a gradient can be produced by including a selected ionophore in the liposomes and that said ionophore creates a lower inside/higher outside pH gradient. See: col.10, line 50 –col. 11, line 5.

The primary reference teaches liposome-entrapped topotecan as being administered to animals as an intravenous bolus injection and the liposome-entrapped topotecan formulation as decreasing tumor volume and in some instances, complete remission of tumor mass. See: col. 16, line 49 – col. 18, line 33. The reference describes how the liposome-entrapped topotecan has a significantly longer circulation time that the free form of the drug. Figures 4A and 4B show lipo-topotecan as remaining in the blood plasma in detectible concentrations for up to 72 hours post administration as compared to free topotecan remaining in the blood plasma in detectible concentrations for only about 2 hours post administration. See: col. 23, line 6 – col. 24, line 30.

Although the primary reference teaches liposome-encapsulated camptothecin and its analogs, including topotecan, and said liposomes as being administered as an intravenous bolus injection for reducing tumor size, the primary reference does not specifically teach the dosage of instant claims 1, 5, 17, and 22-23, the ratio of sphingomyelin to cholesterol of instant claim 4, and the methods of treatment of instant claims 18-21.

While the reference is silent with respect to the specific dosage as claimed instantly in claims 1, 5, 17, and 22-23, differences in concentration will not support patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration is critical. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover optimum or workable ranges by routine experimentation.

In the instant case, the primary reference teaches that the skilled artisan would readily recognize that the effective amount of the topoisomerase can vary depending on factors known to those skilled in the art and one skilled in the art would be able to consider such factors and make a determination regarding the effective amount. Therefore, the specific amounts of instant 1, 5, 17, and 22-23 would have been obvious to and easily determined by one having ordinary skill in the art at the time the invention was made, because the skilled artisan would have to find an effective amount based upon factors known to the skilled artisan.

NEXSTAR discloses liposomal camptothecin formulations having improved pharmacokinetics, enhanced efficacy as anti-tumor agents. See: abstract. The secondary reference teaches that cholesterol is known to improve liposomal stability and prevent loss of phospholipid to lipoproteins in vivo. See: page 11, line 21 – page 12, line 12. The secondary reference teaches phospholipid to cholesterol ratios, which overlap those of instant claim 4. Thus, it would have been obvious to one having ordinary skill in the art at the time the invention was made to add cholesterol as taught by both the primary and secondary references in amounts taught by the secondary reference because of the expectation of obtaining a liposomal formulation with improved stability and which prevents phospholipid loss to lipoproteins in vivo.

NEXSTAR teaches the that the growth of tumors associated with all cancers is contemplated by their invention and specifically teach lung cancer, colorectal cancer, breast cancer, thus meeting the specific methods of treatment as claimed instantly in claims 18-21. See: page 16, line 7-16. It would have been obvious to one having

ordinary skill in the art at the time the invention was made to have used liposome-encapsulated camptothecin and camptothecin analogs such as topotecan as taught by Slater et al., to treat the various cancers as taught by NEXSTAR because of the expectation that encapsulated-encapsulated camptothecin and camptothecin analogs such as topotecan would have similar topoisomerase inhibition activities on different types of cell lines and therefore, have tumor suppression activities on different types of cancers.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

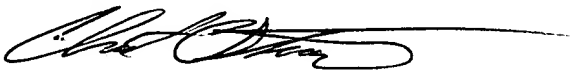
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clinton Ostrup whose telephone number is (703) 308-3627. The examiner can normally be reached on 8:00am - 4:30pm.

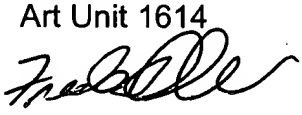
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel can be reached on (703) 308-4725. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Clinton Ostrup
Examiner
Art Unit 1614



Frederick Krass
Primary Examiner
Art Unit 1614



April 3, 2003